

RESEARCH

Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIa lung cancer: observational cohort study

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Abstract

Objective To compare the survival and risk of serious adverse events in older patients with stages II-IIIa non-small cell lung cancer treated with or without postoperative platinum based chemotherapy.

Design Observational cohort study.

Setting Cases of lung cancer in Surveillance Epidemiology and End Results registry linked to Medicare files, 1992-2005, and follow-up data to December 2007.

Participants 3324 patients aged more than 65 years with resected stages II-IIIa lung cancer.

Main outcome measures Primary outcome was overall survival and secondary outcome was the rate of serious adverse events among older patients treated with or without adjuvant chemotherapy.

Results Overall, 21% (n=684) of patients received platinum based chemotherapy. Analyses adjusted, stratified, or matched by propensity scores showed that chemotherapy was associated with improved survival (hazard ratio range 0.78-0.81). The beneficial effect of chemotherapy was also observed among patients treated with radiation therapy (0.75-0.77) or without radiation therapy (0.74-0.77); however, chemotherapy was not beneficial for patients aged 80 or more (1.32-1.46). Adjuvant chemotherapy was associated with an increased odds of serious adverse events (odds ratio 2.0, 95% confidence interval 1.5 to 2.6).

Conclusions Platinum based adjuvant chemotherapy is associated with reduced mortality and increased risk of serious adverse events in older patients with stages II-IIIa lung cancer. The magnitude of the benefit is

similar to that observed in randomised controlled trials carried out among selected patients.

Introduction

Lung cancer is predominately a disease of older people, with the median age at diagnosis in the United States being 69 years.¹ By 2030 an estimated 20% of the US population will be older than 65.² Given the increasing life expectancy and the higher incidence of lung cancer in older people, the management of such patients with resectable non-small cell lung cancer should become increasingly common in clinical practice.

About 40% of patients with non-small cell lung cancer present with stages I to IIIa disease, which may be amenable to resection and is potentially curable.^{3,4} Patients with stage I non-small cell lung cancer have five year survival rates of around 70% and are usually observed after surgical resection.⁵ Conversely, 40-65% of patients with stage II or IIIa disease who have undergone resection experience recurrence and may ultimately die from disease progression.⁶ Several phase III randomised controlled trials have shown the benefit of adjuvant platinum based chemotherapy in patients with stages II-IIIa non-small cell lung cancer.^{7-9,10} Recent meta-analyses of these trials also showed a survival advantage of adjuvant platinum based chemotherapy.¹¹⁻¹⁵ As a result, current guidelines recommend the use of adjuvant chemotherapy as the standard of care for patients with stages II-IIIa non-small cell lung cancer who have undergone resection.¹⁶

Randomised controlled trials of cancer are carried out under highly standardised protocols. Although the internal validity of these trials is strong, the generalisability of the results to older patients with lung cancer is unclear. Most of the studies evaluating the efficacy of adjuvant chemotherapy in non-small cell lung cancer enrolled highly selected participants with good functional status and a low number of comorbidities; thus including a limited number of older participants.^{7 9 10 17 18} Consequently, the observed benefit and adverse effects of adjuvant chemotherapy in these randomised controlled trials may not reflect those expected for older patients treated in routine clinical practice. This lack of evidence on the effectiveness of adjuvant chemotherapy in older patients and concerns about greater risks of adverse events might lead to under-treatment and increased lung cancer mortality among such patients with non-small cell lung cancer.

We used data from the Surveillance Epidemiology and End Results (SEER) registry, a nationally representative, population based data source on cancer, linked to Medicare files to compare survival outcomes and rates of serious adverse events among older patients with stages II-IIIa non-small cell lung cancer treated with or without platinum based adjuvant chemotherapy in routine clinical practice.

Methods

The study was carried out with the 2009 release of the SEER-Medicare linked database, which includes cases of lung cancer diagnosed up to 2005 and follow-up data to December 2007. The SEER registry keeps a national database that collects information on all incident cases of cancer in selected areas of the United States, covering nearly 26% of the US population.¹⁹ From the SEER-Medicare database we selected patients aged more than 65 years with a diagnosis of stages II-IIIa non-small cell lung cancer between 1992 and 2005 and who underwent surgical resection (lobectomy or pneumonectomy). Among these cases we excluded patients in healthcare maintenance organisations or those without part B Medicare insurance (coverage for outpatient care) for whom we were not able to ascertain comorbidities and use of chemotherapy.²⁰ We also excluded patients who died during the perioperative period (within 30 days of surgery) or who were discharged to a nursing home after surgery, as they would have not been candidates for adjuvant chemotherapy. The final cohort consisted of 3324 patients with stages II-IIIa non-small cell lung cancer.

From the SEER-Medicare database we obtained sociodemographic information on characteristics such as age, sex, race or ethnicity, marital status, and estimated income. To evaluate the burden of comorbidities, we used the Deyo adaptation of the Charlson comorbidity index, applying lung cancer specific condition weights as described in the literature.²¹⁻²³ From the SEER database we obtained data on tumour location, size, extension, involvement of lymph nodes, and histology. We classified histological subtypes into categories of adenocarcinoma, bronchioalveolar carcinoma, squamous cell carcinoma, large cell carcinoma, and other histological type.

We examined surgical treatment using information from the SEER-Medicare database.²⁴ Using these data, we classified patients as having either a lobectomy or a pneumonectomy (SEER site specific surgical codes 30 to 70). From Medicare inpatient, outpatient, and physician files we identified those patients who experienced postoperative complications (extrapulmonary infections, cardiovascular complications, thromboembolic events, respiratory complications, reoperations, and transfusions) within 30 days of surgery.²⁵⁻²⁷

Use of radiation therapy was ascertained from the SEER database and Medicare claims. We classified patients as having received radiotherapy if they were coded in the SEER database as having received external beam radiation or if Medicare claims contained any code indicating use of radiation therapy within six months of cancer diagnosis. From Medicare files we identified patients treated with adjuvant chemotherapy. Using validated algorithms, we classified patients as being treated with chemotherapy if Medicare inpatient, outpatient, or physician claims contained any code indicating that the patient received platinum based chemotherapy within three months of surgery.²⁸

Functional status is an important determinant of chemotherapy use. Although the SEER-Medicare database does not include information on patients' functional status, all the study participants were eligible for surgery, which should have effectively excluded patients with poor functional status. To indirectly assess patients' postoperative functional status, we used data from the Home Health Agency file to ascertain use of home health services such as home health aide, physiotherapy, speech therapy, occupational therapy, and medical social services. As beneficiaries must be homebound to be eligible for Medicare home services, we used this information as a proxy for poor functional status.

The primary study outcome, determined from Medicare data, was overall survival. Using information in the Medicare file we calculated survival times as the period from surgery to the date of death. We classified those surviving past 31 December 2007 (alive at the end of follow-up) as censored observations. The secondary study outcome was the rate of serious adverse events among older patients who did or did not receive adjuvant chemotherapy. Using a published algorithm, we defined serious adverse events as those requiring admission to hospital within 2-6 months of surgery (the usual period for occurrence of chemotherapy related adverse events). Serious adverse events were infection, fever, neutropenia, anaemia, thrombocytopenia, dehydration, nausea or emesis, acute renal dysfunction, and unspecified adverse events of systemic therapy.²⁹ Additionally, we evaluated the number of patients who died within 12 weeks of initiation of chemotherapy (the typical duration of platinum based regimens) and number of patients with a diagnosis of neuropathy, a potential long term adverse event from chemotherapy, within two years of resection.

Statistical analysis

The χ^2 test was used to evaluate differences in the distribution of baseline characteristics between patients who did or did not receive postoperative platinum based chemotherapy. We used propensity score methods to control for potential selection bias. The propensity score is a measure of the probability that a patient will receive adjuvant chemotherapy after resection on the basis of their baseline characteristics. We calculated propensity scores using a logistic model that included the patients' sociodemographic characteristics, comorbidities, and cancer related factors (tumour location, size, involvement of lymph nodes, and grade). Additionally, we included dummy variables in the propensity score model indicating whether the patients had postoperative complications or received home services, as these patients were probably less likely to receive adjuvant chemotherapy. Once the model was fitted, we used regression analysis to evaluate whether baseline covariates were balanced across study groups after adjusting for the estimated propensity scores.

To compare survival of patients who did or did not receive adjuvant chemotherapy we used Cox regression analysis

adjusting for propensity scores in three ways.^{30 31} Firstly, we included the propensity score as a continuous covariate in a Cox model comparing the survival of patients treated with and without chemotherapy. In a second approach we fitted a stratified Cox model according to fifths of propensity scores. Finally, we matched patients based on the propensity scores and compared the survival of patients treated with and without adjuvant chemotherapy using a marginal Cox model for correlated data.³² Adjuvant chemotherapy may be used in combination with postoperative radiotherapy. As radiotherapy is usually given concurrently or after chemotherapy this covariate was not included in the propensity score model. Thus we carried out secondary analysis adjusting for and stratifying the cohort by radiotherapy use to assess the effectiveness of chemotherapy among patients treated with and without postoperative radiotherapy. We also did secondary analyses to assess survival among patients treated with and without adjuvant chemotherapy separately for stage II and stage IIIA disease, and within strata according to the patients' age at diagnosis (<70, 70-79, and >80 years). Finally, we repeated all the analyses controlling for year of diagnosis, to adjust for potential time trends in other aspects of lung cancer care.

The potential association of chemotherapy with increased survival may be confounded by the patients' functional status, an important determinant of treatment. To evaluate this possibility we carried out a sensitivity analysis to test whether differences in functional status could account for the magnitude of the observed association of postoperative chemotherapy with survival.³³ In our analysis we used published data on the prevalence of poor functional status (Eastern Co-operative Oncology Group functional status >2) among patients with stages II-IIIa non-small cell lung cancer and the relative hazard of death associated with poor functional status, to evaluate the robustness of our findings across different scenarios.^{34 35}

We calculated the unadjusted odds for serious adverse events, with 95% confidence intervals, for patients receiving adjuvant chemotherapy. To estimate the odds of serious chemotherapy related adverse events among patients receiving chemotherapy compared with those not receiving chemotherapy we used logistic regression analysis after adjusting for propensity scores. All analyses were done with SAS software and using two tailed P values.

Results

From SEER-Medicare database 3759 patients aged more than 65 with resected stage IIA, IIB, or IIIA non-small cell lung cancer were identified. Overall, 435 patients were excluded: 114 had undergone limited resection and 321 were discharged to a long term care facility; the final cohort consisted of 3324 patients with non-small cell lung cancer. In total, 684 (21%, 95% confidence interval 19% to 22%) patients received platinum based chemotherapy. The median follow-up time was 39 months. Table 1 shows the baseline characteristics of these patients. Those treated with adjuvant chemotherapy were younger ($P=0.02$) and more likely to be white ($P=0.04$) and married ($P=0.001$). The characteristics of tumours (histology and stage) also differed significantly between patients treated or not treated with adjuvant chemotherapy ($P=0.005$ and $P<0.001$, respectively). Patients who did not receive adjuvant chemotherapy had a higher burden of comorbidities ($P=0.05$) and were more likely to receive home services ($P=0.04$). Use of postoperative radiotherapy was more common among patients receiving adjuvant chemotherapy ($P<0.001$). Except for postoperative use of radiotherapy, all other covariates were well

balanced among patients treated with and without adjuvant chemotherapy after adjustment for propensity scores (table 1).

Analyses using a Cox model that included the propensity score as a covariate showed that adjuvant chemotherapy was associated with significantly better overall survival (hazard ratio 0.80, 95% confidence interval 0.72 to 0.89; table 2). Five year adjusted survival rates were 35% (95% confidence interval 32% to 39%) for patients treated with adjuvant chemotherapy compared with 27% (25% to 29%) for patients not treated. Patients who received adjuvant chemotherapy also had significantly better overall survival in analysis adjusting for radiotherapy use (hazard ratio 0.77, 95% confidence interval 0.69 to 0.85) or when the analysis was limited to patients who were treated with radiotherapy (0.77, 0.68 to 0.88) and without radiotherapy (0.77, 0.64 to 0.91). The results remained unchanged when the analysis was restricted to patients with stage II (0.71, 0.60 to 0.83) and stage IIIA disease (0.88, 0.77 to 1.00). Analyses within age strata showed that adjuvant chemotherapy was associated with improved survival among patients aged less than 70 years (0.74, 0.62 to 0.88) and 70-79 years (0.82, 0.71 to 0.94); however, the survival benefit was not observed among patients aged more than 80 years (1.33, 0.86 to 2.06). The survival advantage of patients treated with chemotherapy persisted when the analyses were repeated using stratification or matching of study participants by propensity scores. Secondary analyses also showed that adjuvant chemotherapy was associated with improved survival after adjusting for year of diagnosis to control for potential trends in lung cancer treatment.

Sensitivity analyses showed that potential differences in the prevalence of poor functional status among patients treated with and without chemotherapy did not seem to explain the association between platinum based chemotherapy and survival. The adjusted association between adjuvant chemotherapy and improved survival persisted even if untreated patients were five times more likely to have a poor functional status and the hazard ratio for poor functional status was 1.5 (adjusted hazard ratio 0.88, 95% confidence interval 0.79 to 0.9; table 3), or poor functional status was almost three times more common among untreated patients and the mortality risk for patients with poor functional status was twice that of patients with good functional status (0.89, 0.80 to 0.99; table 3).

Overall, 21 patients (3.1%) died within 12 weeks after initiation of chemotherapy. Table 4 shows the percentage of older patients treated with or without adjuvant chemotherapy who were admitted to hospital for the diagnoses that might occur as a serious adverse event. Among patients treated with chemotherapy, 13.0% were admitted to the hospital for at least one of these diagnoses compared with 6.9% of patients who did not receive chemotherapy (odds ratio 2.0, 95% confidence interval 1.5 to 2.6). The most common serious adverse events resulting in admissions to hospital among patients treated with adjuvant chemotherapy were anaemia (8.6%, $n=59$), dehydration (6.7%, $n=46$), and infection (5.3%, $n=36$). Patients who received chemotherapy also had an increased risk of admission to hospital for infection (1.8, 1.2 to 2.7), neutropenia (15.6, 7.1 to 34.1), dehydration (1.8, 1.3 to 2.7), nausea or emesis (2.9, 1.5 to 5.8), anaemia (3.1, 2.2 to 4.4), thrombocytopenia (5.1, 1.1 to 23.1), and unspecified adverse events of systemic therapy (47.1, 6.1 to 363.1). The frequency of admissions to hospital for fever (1.7, 0.5 to 5.6) and renal dysfunction (0.6, 0.2 to 2.1) did not differ significantly. The odds for neuropathy within two years of surgery were also increased among patients treated with chemotherapy (1.4, 1.2 to 1.7). Similar results were obtained in analyses adjusting for propensity scores (table 4).

Discussion

Several randomised controlled trials have shown the efficacy of adjuvant platinum based chemotherapy after resection among patients with stages II-IIIa non-small cell lung cancer.^{9 10 17 18} However, the generalisability of these results to the growing population of older patients with lung cancer is unclear. Using population based data, we found that adjuvant platinum based chemotherapy given to an unselected sample of older patients with stages II-IIIa non-small cell lung cancer in the non-trial setting was associated with a similar improvement in survival. However, patients receiving adjuvant chemotherapy were at increased risk of serious adverse events requiring admission to hospital, and the benefit of adjuvant chemotherapy was not observed among patients aged 80 or more years. Because the net benefits outweighed potential harms, these data should encourage doctors to more strongly consider the use of adjuvant chemotherapy among older patients.

Importance of findings from observational studies

Randomised controlled trials provide the strongest level of evidence on the potential efficacy of cancer treatments such as adjuvant chemotherapy. Patients are randomly allocated to the study arms protecting against potential imbalances in the distribution of prognostic factors among study groups. Consequently, the internal validity of the results of randomised controlled trials is high. Randomised controlled trials are, however, usually carried out in highly controlled settings, such as specialised tertiary care centres, by experienced clinical teams, following standardised protocols, with frequent follow-up visits, and are often limited to select younger patients with few if any major comorbidities. Thus, clinicians may be concerned about extrapolating results from randomised controlled trials to older, sicker patients more often encountered in real world practice settings. Observational data can be useful for assessing the potential benefit of cancer therapies as used in routine clinical practice. In this study we validated the results of randomised controlled trials among a large population based sample of older patients, suggesting that increased use of chemotherapy in this population may improve survival outcomes.

As with other solid tumours, lung cancer primarily affects older people. Despite the high incidence mortality from non-small cell lung cancer in older people, the likelihood of receiving stage appropriate treatment and, in particular, chemotherapy decreases with increasing age.^{36 37} Data from chemotherapy trials designed specifically for older patients with non-small cell lung cancer are lacking; however, there is limited information from post hoc analyses of randomised controlled trials about the potential effectiveness of adjuvant chemotherapy in older people. A retrospective analysis of the adjuvant vinorelbine and cisplatin in elderly patients (JBR.10) trial suggested that the benefit of adjuvant cisplatin based chemotherapy was similar among patients aged 65 or less compared with those who were older.³⁸ Similarly, pooled data from randomised controlled trials of cisplatin based adjuvant chemotherapy also showed similar improvements in overall survival among patients aged less than 65, 65-69, and 70 or more.³⁹ Our results extend these findings by showing that adjuvant platinum based chemotherapy is associated with improved survival in a nationally representative population of Medicare beneficiaries, which included patients with multiple comorbidities or suboptimal functional status. Additionally, our results suggest that adjuvant chemotherapy

is effective when used alone or in combination with radiation therapy.

Comparative effectiveness research based on observational data does not provide the same level of evidence about the benefits of adjuvant chemotherapy as does a randomised controlled trial. In observational studies, decisions about use of adjuvant chemotherapy are influenced by patient preferences, doctors' judgment, and practice patterns. These factors can generate systematic differences in the distribution of prognostic factors among patients treated with and without chemotherapy, which act as confounders of the effect of treatment. However, in this study we used propensity score methods and sensitivity analysis to control for the potential effect of measured and unmeasured prognostic factors. Our analyses showed that adjuvant chemotherapy was associated with a 20% to 25% decreased hazard of death in older people, a survival advantage similar to that reported in meta-analyses of randomised controlled trials.¹⁴ The results of the sensitivity analyses showed that our results were robust to a wide range of assumptions about potential imbalances of the distribution of patients with poor functional status among the two study groups. Analyses carried out within age strata suggest that adjuvant chemotherapy is not associated with improved survival in patients aged 80 or more, thus doctors should carefully weigh up the potential benefits and harms of chemotherapy and discuss these with patients. These results are, however, based on post hoc analyses and the study was not designed or powered to evaluate the effectiveness of chemotherapy in the subgroup of patients aged 80 or more.

A common perception among oncologists is that older patients are at increased risk of serious adverse events from combination chemotherapy regimens including platinum based drugs.⁴⁰ Moreover, given the limited life expectancy of some older patients, concerns are that the possible long term survival benefits of chemotherapy may not offset the potential risk of treatment related complications. Our study shows that adjuvant chemotherapy is associated with an increased risk of serious adverse events requiring admission to hospital. However, the number of deaths within 12 weeks of starting chemotherapy, the type of adverse events observed in our cohort, and the rate of serious adverse event related admissions to hospital were consistent with those reported in previous randomised controlled trials among younger patients.^{7 9 17} Despite the higher rates of admissions to hospital for chemotherapy related serious adverse events, there was a net survival benefit for those who received adjuvant chemotherapy.

Strengths and limitations of the study

Several strengths and limitations of this study should be noted. Firstly, the SEER-Medicare database is a comprehensive source of population based cancer data. Levels of ascertainment within participating areas have been reported to be as high as 98%, indicating most eligible cases are captured in the registry.⁴¹ Additionally, more than 94% of the patients aged 65 or more in the SEER registry are included in the SEER-Medicare database.⁴² Thus our results should be highly generalisable to the older US population as a whole. However, patients aged less than 65 are not eligible for Medicare (except for those with disability or end stage renal disease). Additionally, we excluded patients who were enrolled in a health maintenance organisation or who did not have Medicare part B coverage; thus, we were not able to assess the effectiveness of chemotherapy among these groups.

Patients with stage IIIa non-small lung cancer and with involvement of multiple lymph node stations or bulky

lymphadenopathy are not generally candidates for primary resection and are usually treated with combined chemotherapy and radiotherapy.⁴³ Unfortunately, the SEER registry does not include data on the number of lymph nodes stations involved or the presence of bulky lymph node disease. Although some of these patients may undergo surgery, resection is generally carried out after neoadjuvant chemotherapy or radiotherapy. As we excluded all patients who received neoadjuvant therapy, it is unlikely that patients with multiple or bulky lymphadenopathy were included in the study cohort. Moreover, these patients have a worse prognosis and are more likely to receive postoperative chemotherapy if they undergo resection than patients with less extensive lymph node involvement. Thus, their inclusion would bias our results towards the null.

The SEER-Medicare database is one of the largest available sources of cancer data in the United States. Although the database contains detailed information on the most important prognostic factors for lung cancer, it does not include data on patients' functional status. All patients in the cohort, based on their functional status, were considered fit for surgery. However, other factors (such as organ dysfunction) may also influence doctors' decisions about use of adjuvant chemotherapy in older patients. We adjusted our analyses for some of these potential confounders, such as comorbidities and postoperative complications, and utilised home services use as a proxy for poor functional status. Moreover, sensitivity analyses suggested that potential higher rates of poor functional status among patients who were not treated with adjuvant chemotherapy are unlikely to explain the observed benefit of chemotherapy. Aggressive treatment of older patients with lung cancer can result in serious adverse events; thus, survival benefits may not be accompanied by improvements in quality of life. These concerns may be one of the reasons for lower rates of chemotherapy use among older patients with lung cancer. Although we could not assess the potential impact of chemotherapy on quality of life, multiple studies focusing on older patients and on those with lung cancer or other malignancies showed that most patients are willing to endure a relatively poor quality of life in exchange for increased survival time.⁴⁴⁻⁴⁶ Additionally, studies show that patients with cancer are in general willing to accept intensive chemotherapy and potential adverse effects for a relatively small chance of benefit.⁴⁷⁻⁴⁹

Conclusions and clinical implications

In summary, these data suggest that older patients with resected stages II-IIIa non-small cell lung cancer treated with adjuvant platinum based chemotherapy in routine practice settings have an improved survival compared with those who do not receive chemotherapy. The survival advantage in this patient population is comparable to that observed in younger, highly selected patients enrolled in previous randomised controlled trials assessing the efficacy of adjuvant chemotherapy. However, patients who received chemotherapy in our cohort were at increased risk of serious adverse events requiring admission to hospital; a factor that can negatively impact quality of life. Thus doctors should discuss the potential benefits and disadvantages of adjuvant chemotherapy with older patients who have lung cancer before initiating treatment. Given the rapid increase in the older population with lung cancer, our findings suggest that more frequent use of adjuvant platinum based chemotherapy in this patient population may improve patients' survival outcomes.

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What is already known on this topic

Randomised controlled trials have shown the efficacy of adjuvant chemotherapy for stage II-IIIa non-small cell lung cancer

What this study adds

Using data from a population based cancer registry, we showed that adjuvant chemotherapy is associated with improved survival among older patients with lung cancer treated in the community

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Tables

Table 1 | Baseline characteristics of patients with stages II-IIIa non-small cell lung cancer in Surveillance Epidemiology and End Results-Medicare database, 1992-2005. Values are numbers (percentages) unless stated otherwise

Characteristic	Adjuvant chemotherapy (n=684)	No adjuvant chemotherapy (n=2640)	P value	
			Not adjusted for propensity scores	Adjusted for propensity scores
Mean (SD) age (years)	71.5 (4.3)	73.4 (5.1)	0.02	0.96
Women	304 (44)	1181 (45)	0.89	0.99
Race or ethnicity:				
White	609 (89)	2323 (88)	0.04	0.98
African-American	44 (6)	129 (5)		
Hispanic	—*	35 (1)		
Other	—	152 (6)		
Married	465 (68)	1615 (61)	0.001	0.98
Median income in area of residence:				
Lowest fourth	137 (20)	617 (23)	0.21	0.98
Second fourth	177 (26)	681 (26)		
Third fourth	167 (25)	639 (24)		
Highest fourth	201 (29)	696 (27)		
Comorbidity score†:				
0-1	313 (46)	1065 (40)	0.05	0.99
>1-1.5	222 (32)	898 (34)		
>1.5-2.5	56 (8)	266 (10)		
>2.5	93 (14)	411 (16)		
Home services	437 (17)	91 (13)	0.04	0.96
Histology:				
Adenocarcinoma	374 (55)	1251 (47)	0.005	0.98
Bronchioloalveolar cell carcinoma	39 (6)	163 (6)		
Squamous cell carcinoma	209 (31)	956 (36)		
Large cell carcinoma	32 (4)	172 (7)		
Other	30 (4)	98 (4)		
Tumour location:				
Upper lobe	378 (55)	1483 (56)	0.40	0.95
Middle lobe	27 (4)	105 (4)		
Lower lobe	231 (34)	913 (35)		
Other	48 (7)	139 (5)		
Cancer stage:				
IIA	80 (12)	362 (14)	<0.001	0.98
IIB	216 (32)	1024 (39)		
IIIA	388 (56)	1254 (48)		
Type of surgery:				
Lobectomy	604 (88)	2256 (85)	0.06	0.99
Pneumonectomy	80 (12)	384 (15)		
Postoperative radiation:				
Yes	417 (61)	1172 (44)	<0.001	—‡
No	267 (39)	1468 (56)		

*Exact numbers not reported to maintain patient confidentiality.

†Deyo adaptation of Charlson comorbidity index.²¹⁻²³

‡Radiation not included in propensity score model as it is not a pre-treatment characteristic.

Table 2| Comparison of survival in patients treated with and without adjuvant chemotherapy using propensity score analysis

Model	Hazard ratio (95% CI)	
	Not adjusted for radiation therapy	Adjusted for radiation therapy
Primary analysis		
Entire cohort:		
Adjusting for propensity scores	0.80 (0.72 to 0.89)	0.77 (0.69 to 0.85)
Stratified by propensity score fifths	0.81 (0.73 to 0.89)	0.77 (0.69 to 0.85)
Matched analysis	0.78 (0.70 to 0.87)	0.74 (0.66 to 0.82)
Secondary analyses		
Patients treated with radiation:		
Adjusting for propensity scores	0.77 (0.68 to 0.88)	—
Stratified by propensity score fifths	0.77 (0.68 to 0.88)	—
Matched analysis	0.75 (0.66 to 0.86)	—
Patients not treated with radiation:		
Adjusting for propensity scores	0.77 (0.64 to 0.91)	—
Stratified by propensity score fifths	0.76 (0.64 to 0.91)	—
Matched analysis	0.74 (0.62 to 0.89)	—
Stage II disease:		
Adjusting for propensity scores	0.71 (0.60 to 0.83)	0.67 (0.57 to 0.79)
Stratified by propensity score fifths	0.70 (0.60 to 0.83)	0.66 (0.56 to 0.78)
Matched analysis	0.70 (0.60 to 0.83)	0.67 (0.56 to 0.78)
Stage IIIA disease:		
Adjusting for propensity scores	0.88 (0.77 to 1.00)	0.85 (0.74 to 0.98)
Stratified by propensity score fifths	0.89 (0.78 to 1.02)	0.86 (0.75 to 0.98)
Matched analysis	0.86 (0.75 to 0.98)	0.83 (0.72 to 0.95)
Age <70 years:		
Adjusting for propensity scores	0.74 (0.62 to 0.88)	0.72 (0.60 to 0.86)
Stratified by propensity score fifths	0.75 (0.63 to 0.90)	0.73 (0.61 to 0.87)
Matched analysis	0.76 (0.63 to 0.90)	0.72 (0.61 to 0.86)
Age 70-79 years:		
Adjusting for propensity scores	0.82 (0.71 to 0.94)	0.78 (0.68 to 0.89)
Stratified by propensity score fifths	0.83 (0.73 to 0.96)	0.78 (0.69 to 0.90)
Matched analysis	0.82 (0.71 to 0.93)	0.77 (0.67 to 0.89)
Age ≥80 years:		
Adjusting for propensity scores	1.33 (0.86 to 2.06)	1.24 (0.80 to 1.99)
Stratified by propensity score fifths	1.32 (0.84 to 2.05)	1.22 (0.78 to 1.90)
Matched analysis	1.46 (0.91 to 2.34)	1.29 (0.80 to 2.08)

Table 3| Sensitivity analysis of potential effect of poor functional status on effectiveness of adjuvant chemotherapy

Poor functional status (%)*		Hazard ratio for poor functional status†	Hazard ratio for chemotherapy adjusted for functional status (95% CI)
No chemotherapy	Chemotherapy		
15	5	1.5	0.84 (0.76 to 0.93)
25	5	1.5	0.88 (0.79 to 0.98)
20	7.5	1.5	0.85 (0.76 to 0.94)
25	7.5	1.5	0.87 (0.78 to 0.97)
25	15	1.5	0.84 (0.75 to 0.93)
40	25	1.5	0.85 (0.77 to 0.95)
15	5	1.75	0.86 (0.77 to 0.95)
20	7.5	1.75	0.87 (0.78 to 0.97)
25	7.5	1.75	0.90 (0.81 to 1.00)
25	15	1.75	0.85 (0.76 to 0.95)
40	25	1.75	0.88 (0.79 to 0.97)
15	5	2.0	0.87 (0.79 to 0.97)
20	7.5	2.0	0.89 (0.80 to 0.99)
25	7.5	2.0	0.93 (0.84 to 1.03)
25	15	2.0	0.87 (0.78 to 0.97)
40	25	2.0	0.90 (0.81 to 0.99)

*Functional status according to Eastern Co-operative Oncology Group functional status >2.

†Compared with good functional status.

Table 4| Admissions to hospital for chemotherapy related serious adverse events among study participants

Adverse events	No (%) of patients admitted with adverse event		Odds ratio (95% CI)	Odds ratio (95% CI) adjusted for propensity scores
	Adjuvant chemotherapy	No adjuvant chemotherapy		
Infection	36 (5.3)	79 (3.0)	1.8 (1.2 to 2.7)	2.0 (1.3 to 3.1)
Neutropenia	>30 (>4.4)	≤11 (<1)*	15.6 (7.1 to 34.1)	17.1 (7.6 to 38.1)
Fever	≤11 (≤1.6)	≤11 (<1)*	1.7 (0.5 to 5.6)	1.6 (0.4 to 5.7)
Dehydration	46 (6.7)	97 (3.6)	1.8 (1.3 to 2.7)	1.9 (1.3 to 2.8)
Nausea or emesis	15 (2.1)	20 (0.8)	2.9 (1.5 to 5.8)	2.6 (1.2 to 5.3)
Anaemia	59 (8.6)	78 (3.0)	3.1 (2.2 to 4.4)	3.6 (2.5 to 5.2)
Thrombocytopenia	≤11 (≤1.6)	≤11 (<1)*	5.1 (1.1 to 23.1)	8.3 (1.7 to 40.4)
Renal dysfunction	≤11 (≤1.6)	19 (0.6)	0.6 (0.2 to 2.1)	0.7 (0.2 to 2.4)
Unspecified adverse events of systemic therapy	≥11 (≥1.7)	≤11 (<1)*	47.1 (6.1 to 363.1)	79.7 (9.9 to 635.9)

*Exact numbers not reported to maintain patient confidentiality.